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IS PASSIVE SMOKING A CAUSE OF ASTHMA IN CHILDHOOD?

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Abstract

There is growing evidence, although not wholly consistent, that maternal smoking is a risk factor for asthma and wheezing illness in childhood. The epidemiological evidence for this association is reviewed including considerations of study design, misclassification and confounding. While the timing and mechanism of this effect, whether prenatal or postnatal, are not yet known, it is concluded that there is sufficient evidence for public health purposes to target maternal smoking as a modifiable risk factor for wheezing illness in childhood.

Key words: Environmental tobacco smoke, passive smoking, epidemiology, asthma, child health

Introduction

The association between passive smoking and childhood asthma is currently the object of considerable and growing interest. Earlier reviews of the subject, while providing good evidence for an association between maternal smoking and lower respiratory illness in children under two years of age [1–7], were unable to deduce an association between passive smoking and asthma or wheezing in childhood with any confidence, in view of a number of negative or equivocal studies [8–13].

However, in the light of reports of an increase in asthma prevalence, hospital admissions and mortality among young people in a number of countries in recent years [14–19], indoor air pollutants such as passive smoking have been identified as potential contributors to such trends [19]. A possible causal association between passive smoking and childhood asthma would thus be of considerable public health importance.

Such an association has biological plausibility, especially if one includes the effects of smoking on the foetus *in utero* under the broad heading of passive smoking. *In utero* effects of nicotine and maternal smoking on the foetal rodent respiratory system have been produced experimentally [20,21], while increased IgE levels have been reported in the newborns of smoking mothers [22]. Inhalational effects on young children leading to an asthmatic response can also be postulated, as environmental tobacco smoke (ETS) may initiate inflammatory or immunological processes in airway walls, for example by increasing epithelial permeability [23]. Episodic airway narrowing in response to allergens, irritants or infection may be

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mediated by an increased prevalence or tendency to non-specific bronchial hyperresponsiveness, IgE levels or atopy [24,25] or mucus hypersecretion associated with exposure to ETS [26].

Although increases in bronchial hyperresponsiveness [27,28] and IgE levels [29,30] have been shown among active smokers, active smoking does not appear to be a strong predictor of asthma [31,32]. However, asthmatics may be less likely to smoke, or more likely to quit smoking, thus obscuring an underlying aetiological association.

The number of epidemiological studies of the association between passive smoking and asthma and wheezing in children is growing and the aim of this review is to re-examine the epidemiological evidence. Because of underdiagnosis of asthma [33] and the difficulties of defining asthma for epidemiological purposes [34], wheezing [35] as well as non-specific bronchial hyperresponsiveness are included as outcomes of interest, although they may lack some specificity for clinical asthma. For purposes of exposition, the epidemiological studies are divided according to the type of population studied, *viz.* general population studies and studies of asthmatics using health services. These in turn are further grouped according to study design.

General population studies

Prospective general population studies offer the advantages of establishing the parental smoking habit in advance of the disease, including the opportunity for repeated measurement of smoking, and for reducing recall bias by parents of asthmatic or wheezing children. There are now a fair number of large prospective studies which have investigated the assocation between passive smoking and asthma or wheezing.

Early studies in this category found no association between parental smoking and asthma [12,13] or an association with wheezing only if both parents smoked [8]. More recent prospective studies that have separated maternal smoking from other sources of passive smoking have generally been able to show an effect, although again not in all subgroups examined. Thus, an association has been demonstrable in various ways for wheezing illness but not asthma [36,37], among children of less educated mothers only [38], or only in younger children [39]. Studies of wheezing illness in infants [40,41] have strengthened other findings regarding early lower respiratory tract illness [42,43], by showing that maternal smoking increases the risk of such wheezing episodes.

Cross-sectional general population studies are less onerous and expensive to mount than prospective studies and, therefore, more numerous, but suffer the disadvantage of collecting symptom or illness information contemporaneously with smoking data. Parents of symptomatic children may alter their smoking habits or may report such habits differently from parents of asymptomatic children. Further, unless smoking habits are constant or the aetiological impact ongoing, current smoking may be a poor indicator of a relevant causal exposure occurring some years earlier.

As with prospective studies, there has been considerable variability of results among those cross-sectional studies that did not distinguish between maternal and other sources of smoking. Some such studies have been clearly positive [44,45] but a number have reported no association between parental smoking and asthma or wheeze [10,11,46,47]. Others have been marginally positive [48], have demonstrated an association with wheeze but not asthma [49,50], in one sex only [51,52], among English but not Scottish children [52] or only if a co-factor such as dampness at home was also present [53].

In those cross-sectional studies which examined maternal smoking as a separate variable, the evidence is more strongly consistent for an association with asthma [54–57] and for wheezing [58]. In addition, Ekwo *et al.* [59] found an association between maternal smoking and 'wheezing with colds' but not 'wheezing without colds'. Martinez *et al.* [24] reported an association with bronchial hyperresponsiveness among boys but not girls. Only Schenker *et al.*

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found no relationship between maternal smoking and asthma or wheezing, while O'Connor *et al.* [60] could demonstrate an association of maternal smoking with bronchial hyperresponsiveness only in the subgroup of asthmatic children in their sample.

Studies of asthmatics

Asthmatic populations may be drawn from a hospital or clinic, or identified as part of a general population study. Case control studies, in which asthmatics are compared to some non-asthmatic group, test the same hypothesis as the studies in the previous section, *i.e.* whether asthma occurrence is associated with passive smoking. Studies of asthmatics without a control group, on the other hand, investigate whether passive smoking aggravates the asthmatic state.

There have been a number of case-control studies in which the cases were drawn from a clinic or hospital [61–65]. Of these, three have found a positive association between some measure of parental smoking and asthma [62–64]. These studies have generally been small, and must be interpreted carefully because of the impact of various biases which may operate through differences between cases and controls in the way they are selected, in the manner they are questioned, and in the accuracy of recall of smoking and of potential confounders. For example, of the above studies, three [61–63] made no adjustment for confounders.

Of interest is that three of the hospital-based case-control studies used urinary cotinine as a biomarker of exposure: two found significant differences in cotinine levels between asthmatics and controls [63,64] and one no difference [65]. While cotinine is a potentially useful marker of passive smoking in asthma studies, a single reading appears to be subject to a variety of influences other than the reported level of passive smoking in the home, and there are a number of methodological questions regarding its use which remain to be resolved [64,66,67].

There have been few studies of the effect of maternal smoking among diagnosed asthmatics. Murray and Morrison [68–70] have shown that asthmatic children whose mothers smoke have worse symptoms and lung function and greater bronchial hyperresponsiveness than asthmatic children whose mothers do not smoke. Corroboration of these findings has come from general population studies in which, among the subgroup of children with parent-reported asthma, bronchial hyperresponsiveness was increased if there was a smoking mother or parent [24,60,71]. Asthmatics exposed to smoking at home also seem to have more frequent visits to the emergency room than those without such exposure [72].

Discussion

Despite inconsistency among the studies reviewed, a coherent pattern is emerging. In particular, studies which have been able to separate out maternal smoking have been more consistently positive than those that did not make this distinction. Further, among the studies which quantified maternal smoking [13,36,40,55,58,69], nearly all have been able to show some exposure-response relationship between maternal smoking and some measure of asthma or wheeze.

The relative risk or odds ratio in the larger studies which controlled to some degree for confounding has been modest, of the order of 1.5 [36,39,54,57,58]. In contrast, most studies have failed to show an effect of paternal smoking.

This maternal predominance may reflect *in utero* influences, the child's inhalational exposure to ETS from maternal sources, or both. It is difficult to separate these influences epidemiologically as mothers who smoke in pregnancy can be expected to continue after the child is born.

Measurement of lung function in neonates has allowed the application of the tools of epidemiology to investigate the effect of *in utero* (or at least very early postnatal) exposure. Diminished lung function [73] and increased non-specific bronchial hyperresponsiveness [74] have been shown in infants of mothers who smoked in pregnancy. Further, early lung function decrement has been shown to predict the likelihood of early

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wheezing lower respiratory illness [75,76]. Taken with evidence that early lower respiratory infection, particularly bronchiolitis, is a predictor of later wheezing and asthma [77–80], this may be one pathway for the impact of exposure *in utero* or in early neonatal life in the aetiology of asthma. There is also limited evidence of immunological effects *in utero*: there is one report of elevated IgE levels in the cord blood of neonates of smoking mothers [22].

There is probably more than one mechanism underlying the relationship between maternal smoking and asthma, however. The maternal predominance may reflect the closer association between smoking mothers and young children in the home environment, and the greater role of maternal smoking in the ETS exposure of the child. This has been corroborated by studies using cotinine as a marker of exposure, which have been able to show a greater contribution to nicotine absorption by the child if the mother was the only smoker compared to that of lone paternal smoking [81–84].

In general, the evidence for an effect of passive smoking on wheezing and other lower respiratory illness is more consistent for children under two years of age than that for older children. To the extent that this is due to postnatal exposure it suggests that such exposure in the first few years of childhood may be more critical, or alternatively more intense, than later exposure to maternal ETS. However, there is evidence for at least some ongoing effect of maternal smoking on the incidence of wheezing [37] or asthma severity [70] in older children.

There is also consistent evidence that among children already asthmatic, maternal smoking is associated with more severe asthma [68–70], more frequent visits to the emergency room [72] and greater bronchial hyperresponsiveness [24,60,68–71].

Regarding the timing of the effect, Frischer *et al.* [71] found reported maternal smoking in infancy to be more closely associated with bronchial hyperresponsiveness among eight-year-old asthmatics than was current maternal smoking. In contrast, in Murray's report [69], seasonal variation in bronchial hyperresponsiveness seemed to be related to the degree of contemporaneous exposure to maternal smoking.

Although commonly held to be an irritant for some asthmatics and a modifiable cause of asthma attacks [61] there has been little direct testing of the hypothesis that passive smoking triggers asthmatic attacks in children. Clinical laboratory studies of children [85] and young adults have been inconsistent [86–90]. Objective hypersensitivity to tobacco antigens has also not been shown to be associated with eye, nasal and bronchial symptoms among individuals reporting themselves to be sensitive to ETS [91].

Despite the emerging evidence concerning the importance of maternal smoking, variation remains among study findings, and this is likely to continue. Part of this variation between studies is due to the difficulties of measuring accurately the child's true dose of smoke exposure. Furthermore, ETS is a complex mixture of agents [92], any or a number of which may be implicated.

However, misclassification of the child's 'true' exposure is unlikely to produce spurious positive findings. In general, such misclassification will be random, i.e. uninfluenced by whether the child has asthma or not and will move the study findings in the direction of no association. Non-random misclassification could conceivably arise in certain circumstances, for example, if parents of asthmatics deny their smoking. The effect of this, however, will also make it more difficult to observe a positive association.

Similarly, misclassification of children with respect to the outcome, wheezing or asthma, is likely to occur. There is no epidemiological gold standard for asthma [34] and differences between studies will arise merely because they use different definitions of asthma or wheezing. However, there has been some standardisation, based particularly on use of the American Thoracic Society, Division of Lung Disease questionnaire [93] which identifies 'persistent wheezing' as well as doctor-diagnosed asthma. Among studies which used some version of the standard

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questions, there is consistency [37,44, 50,52,58], although not unanimity [11].

Could the positive association found in a number of studies be accounted for by confounding? This is a consideration wherever the measure of effect is modest. Important potential confounders that have been identified are socioeconomic status (SES), parental symptoms and active smoking in childhood.

SES is an indicator of a wide range of influences which affect health. Children of lower SES may be subject to other air pollutants, poorer housing quality and nutrition, and less access to decent health care than children who are well off. To the extent that these factors individually or collectively increase the risk of asthma, and in addition are more common among the children of smokers, they may produce an exaggerated relationship between passive smoking and asthma, i.e. confounding.

Most studies have found wheezing to be more common among children of lower SES or of less educated parents [8,36,41, 45,58,94], although this is not clearly the case of children who have been diagnosed asthmatic [8,12,54], suggesting a differential likelihood of diagnosis by SES. Passive smoking is also likely to be more common among children of lower SES, although in the United States this varies by ethnic background [95,96]. However, most of the positive studies reviewed have included some variable to denote social class difference, frequently parental education, without eliminating the effect of maternal smoking.

The simultaneous measurement of a number of variables such as family size [97], home dampness [46,53] and maternal care factors [98], might be needed to adjust fully for the range of social class-related influences [94].

The observation that parents who are themselves symptomatic report more respiratory symptoms in their children [8,9,10,11,58] has been interpreted as requiring adjustment for such parental symptoms as a potential confounder [2]. Such adjustment has led to some attenuation but not elimination of the association between parental smoking and asthma or wheezing [9,38,44,51,58]. However, this association between parental and child's symptoms may not be due to overreporting, but to the common direct response to tobacco smoke, to cross-infection in smoking households [96] or to hereditary tendencies in asthma [8,99]. In such cases, adjustment for parental symptoms may result in a degree of overadjustment [4].

Active smoking by the child is another potential confounder in studies of children over about seven years of age, as children of smoking parents are more likely to try smoking themselves. In the positive studies of older children which inquired about active smoking by the child, one [44] controlled for such smoking, another [58] found smoking to be rare among six- to nine-year-olds, while a third [49] found no daily smoking among a subgroup of sixth graders who were questioned. However, underreporting by older children of their smoking habits is probable and some degree of confounding may occur.

Conclusion

The association between maternal smoking and asthma and wheezing illness in children satisfies a number of the criteria for causality [2]. There is reasonable consistency among studies, an exposure-response relationship has been demonstrated and an appropriate temporal relationship established in prospective studies.

In addition, the association has biological plausibility although the mechanism remains to be defined, and there is not strong evidence that confounding accounts for the observed increase in risk.

From a public health perspective the impact of such a causal relationship is considerable. Assuming a relative risk of asthma due to maternal smoking of 1.5, after controlling for confounding, and a maternal smoking prevalence of 30% [95], an attributable proportion of 13% can be calculated [100]. This is the proportion of asthma and persistent

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wheeze in childhood that could be prevented in the absence of maternal smoking. This should add further weight to public health, clinical and educational efforts to reduce the burden of illhealth imposed on young children by the tobacco smoking habit.

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